Phase II study of berzosertib + topotecan in patients with relapsed platinum-resistant small-cell lung cancer (DDRiver SCLC 250): Japanese safety run-in

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Background

- Small-cell lung cancer (SCLC) is a highly aggressive, neuroendocrine-derived cancer
- Berzosertib (C785) is a selective ATR inhibitor in development for various cancer indications
- The DDRiver SCLC 250 trial (NCT04768296) was designed to evaluate the efficacy and safety of berzosertib + topotecan in patients with relapsed, platinum-resistant SCLC

Methods

- A total of 21 Japanese patients with relapsed, platinum-resistant SCLC were enrolled
- Berzosertib 210 mg/m² (days 2 and 5) + topotecan 1.25 mg/m² (days 1–5) was administered cycle 1 (21 days) to 12 cycles

Results

- No complete responses were observed
- 3 partial responses were observed, with duration ranging from 3.9 to 8.3 months
- The median progression-free survival (PFS) and overall survival (OS) were 6 months

Conclusions

- Berzosertib + topotecan showed antitumor activity in patients with relapsed, platinum-resistant SCLC
- Further studies with berzosertib in combination with topotecan are warranted

References


**Table 1. Key eligibility criteria**

<table>
<thead>
<tr>
<th>Key eligibility criteria</th>
<th>Key exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese safety run-in, DL1</td>
<td>Japanese safety run-in, DL2</td>
</tr>
<tr>
<td>- Histologically confirmed advanced solid tumor</td>
<td>- Histologically confirmed solid tumor, if disease is progressing on prior platinum-based chemotherapy</td>
</tr>
<tr>
<td>- Karnofsky performance status ≥70%</td>
<td>- Karnofsky performance status ≥70%</td>
</tr>
<tr>
<td>- No active intercurrent illness</td>
<td>- No active intercurrent illness</td>
</tr>
</tbody>
</table>

**Table 2. Objectives and endpoints: Japanese safety run-in**

- To confirm whether the PK of berzosertib + topotecan equips to Japanese patients (primary objective)
- To characterize the pharmacokinetic profile of berzosertib in Japanese patients
- To evaluate the efficacy of berzosertib + topotecan

**Table 3. Baseline characteristics**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>DL1 (n=3)</th>
<th>DL2 (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>2 (66.7)</td>
<td>0</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>61.3 (4)</td>
<td>51.7 (4)</td>
</tr>
<tr>
<td>Tumour type</td>
<td>Platinum-resistant SCLC (n=3)</td>
<td>Platinum-resistant SCLC (n=3)</td>
</tr>
<tr>
<td>Brain metastases present at baseline, n (%)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Liver metastases present at baseline, n (%)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
</tr>
</tbody>
</table>

**Table 4. Safety events**

<table>
<thead>
<tr>
<th>Safety events</th>
<th>DL1 (n=3)</th>
<th>DL2 (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE grade 3 or 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTCAE grade 5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 5. Key plasma berzosertib pharmacokinetic parameters following IV infusion on Cycle 1 Day 5**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>DL1 (ng/mL)</th>
<th>DL2 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>811 (491)</td>
<td>574 (50)</td>
</tr>
<tr>
<td>AUCss</td>
<td>223 (123)</td>
<td>170 (82)</td>
</tr>
</tbody>
</table>

**Effectiveness**

- At all six cut-offs, all four patients with DL1 had disease progression in the patient at each dose level

**Safety**

- Safety results are shown in Table 4. No DLTs were experienced

**Results**

- 3 partial responses were observed, with duration ranging from 3.9 to 8.3 months
- The median progression-free survival (PFS) and overall survival (OS) were 6 months

**Conclusions**

- Berzosertib + topotecan showed antitumor activity in patients with relapsed, platinum-resistant SCLC
- Further studies with berzosertib in combination with topotecan are warranted

**References**


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**Conflict of interest**

The following authors report no conflict of interest: Tatsuya Ishida, Anish Thomas, Roland Hallwachs, Jayaprakasam Bolleddula, Tsukito Kurihara, Camillo Moulin, Luis Paz-Ares. Rebeca Pastor, MD, PhD, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, reports financial support from Merck; and Annette Johnson, PhD, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, reports financial support from Merck and Merck Healthcare KGaA, Darmstadt, Germany. Jayaprakasam B., Anish T., Roland H., and Camillo M. are employees of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA. Tatsuya Y., Noboru Y., and Luis P.-A. are employees of Merck Healthcare KGaA, Darmstadt, Germany. Barbara S. is an employee of AstraZeneca, Boehringer Ingelheim, Chugai, Lilly, Novartis, Bayer and Amgen; been part of a steering committee or an advisory board for AstraZeneca, Boehringer Ingelheim, Chugai, Lilly, Novartis, Merck, BMS, Abbvie, Takeda, MSD, Novartis, Merck, BMS.

**Supplementary material**

Supplementary material is available at the Journal of Clinical Oncology online.

**Author contributions**

Tatsuya Ishida, Anish Thomas, Roland Hallwachs, Jayaprakasam Bolleddula, Tsukito Kurihara, Camillo Moulin, Luis Paz-Ares were responsible for the study concept and design; Tatsuya Ishida, Anish Thomas, Roland Hallwachs, Jayaprakasam Bolleddula, Tsukito Kurihara, Camillo Moulin, Luis Paz-Ares were responsible for the acquisition, analysis, and interpretation of data; Tatsuya Ishida, Anish Thomas, Roland Hallwachs, Jayaprakasam Bolleddula, Tsukito Kurihara, Camillo Moulin, Luis Paz-Ares were responsible for manuscript preparation. All authors had access to the data and had the final responsibility to submit the manuscript.